Manual Therapy, Posturology & Rehabilitation Journal
formerly REVISTA TERAPIA MANUAL

STUDY PROTOCOL

http://dx.doi.org/10.17784/mtprehabjournal.2018.16.569

Inspiratory muscle training in pulmonary hypertension: TREMMI protocol

Marília Souza Leão[1], Lucas Mellaci Bergamascki[1], Vivian Bertoni Xavier[1], Rodrigo Boemo Jaenisch[2], Roberto Stirbulov[1], Vera Lúcia dos Santos Alves[1]

ABSTRACT

Background: Although the progressive nature of pulmonary hypertension (PH), including the impairment of respiratory muscle function, studies have demonstrated beneficial effects of physical exercise on the functional limitations caused by the disease in this population, being an important ally to the conventional drug therapy. There is no training protocol focused exclusively on respiratory musculature that is performed without supervision, since these patients have low adherence to the rehabilitation programs performed in an outpatient setting. Respiratory muscle training (RMT) improves functional capacity and quality of life (QoL) in patients with chronic diseases such as heart failure and COPD. However, the effects of an unsupervised RMT protocol on PH are not yet known. **Objective**: To developed an unsupervised, home-based RMT protocol for patients with PH. **Methods**: A double-blind, controlled, randomized clinical trial to evaluate the effectiveness of this protocol on respiratory muscle strength and endurance, functional capacity, by the six-minute walk test and QoL with the questionnaire The Medical Outcomes Study 36- item Short Form Health Survey (Sf-36) before and after an unsupervised training protocol and performed in a home environment with *POWERbreathe*. Two groups (IMT and SHAM) will be followed for 12 weeks with training performed 30 minutes daily. **Results**: We hope the intervention idealized by the protocol may will increase the respiratory muscle strength and endurance, the walk distance in six-minute walk test and QoL. **Conclusions**: Patients with PH who perform the intervention with inspiratory muscle training protocol may will be increase the respiratory muscle strength, functional capacity and QoL.

Keywords: Functional Capacity, Inspiratory Muscle Training, Pulmonary Hypertension, Quality of Life.

INTRODUCTION

Pulmonary hypertension (PH) is a progressive pathological condition diagnosed by mean pulmonary arterial pressure (PAP) ≥25 mm Hg at rest and diagnosed by right heart catheterization[1-3]. Regardless of etiology, PH presents vascular changes in the lungs that cause proliferative and obstructive remodeling promoting vasoconstriction with consequent increasing of pulmonary vascular resistance (PVR). As the disease progresses, there is an increase in PAP, overloading the right ventricle (RV) resulting in right heart failure and death[3]. Patients with PH have severe functional limitations due to dyspnea, unable to undertake a physical exercise program or do activities of daily living (ADL)[4]. Cardiopulmonary changes in PH are considered the main limiting factor, however, changes on muscles worsen symptomatology[5]. In the early stages, the PH can be asymptomatic; its progression causes fatigue, dyspnea, syncope and angina leading to decreased exercise capacity and quality of life (QoL)[5,6]. Several PH factors and mechanisms have an impact on peripheral and respiratory muscle changes such as decreased cardiac output, hypoxemia, inflammation, increased insulin resistance, altered autonomic nervous system (ANS) response, and muscle disuse. These factors imply on alterations of the fiber type, atrophy, capillary vascular reduction, oxidative capacity reduction, endothelial dysfunction and decreased muscle excitability[7]. Specifically, respiratory muscles are also altered in patients with PH. Studies involving patients with idiopathic PH demonstrated 25% reduction in maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) and a 28% decrease of MIP in patients with PH associated with left heart disease when compared to healthy subjects resulting in a major socioeconomic impact[8,9].

For the treatment of PH, in addition to the drug therapy, studies demonstrated the effects of physical exercises. Although there is no consensus regarding the best exercise modality, duration, frequency or intensity, the physical training promotes benefits in exercise capacity, maximal oxygen capacity (VO_2peak) and QoL. The latest European guideline[10] recommends supervised exercise in patients with PH who are clinically stable

Corresponding author: Vera Lúcia dos Santos Alves; Rua Dr. Cesário Motta Jr, 61, Vila Buarque; CEP: 01221-020 – São Paulo (SP) – Brazil. Phone: +55 11 38721966
E-mail: fisioterapiasc@uol.com.br

[1] Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP), São Paulo, SP, Brazil.

Full list of author information is available at the end of the article.

Financial support: nothing to declare.

Submission date 05 February 2018; Acceptance date 02 April 2018; Publication date 02 July 2018

with optimized drug therapy (evidence grade IIa, Level B), but patients often do not have access to supervised physical rehabilitation programs, which turns its practice a challenge. Regarding the respiratory muscle weakness, inspiratory muscle training (IMT) has been shown to increase respiratory muscle strength and functional capacity in chronic conditions such as chronic obstructive pulmonary disease (COPD) and heart failure (HF)[11,12]. In PH, the study of Saglam M *et al.* demonstrates improvement of respiratory muscle strength and functional capacity, resulting in decreasing of dyspnea and fatigue in PH patients, who performed the IMT protocol during six weeks of outpatient training[13].

The hypothesis is that a inspiratory muscle training (IMTTREMMI) protocol improves functional capacity, QoL and inspiratory muscle strength in patients with PH and that these results remain after three months of the end of training. Our objectives is to assess the effects of TREMMI protocol on functional capacity, respiratory muscle strength, and QoL PH patients.

METHODS

A double-blind randomized, controlled trial with patients in the multi-professional Pulmonary Hypertension Outpatient Clinic of Santa Casa de Misericórdia of São Paulo (São Paulo, Brazil) was conducted. The study participants and the head researcher will be blind as to the group allocation. The randomization will be done by site (https://www.random.org/) that generated the distribution of 24 numbers between 1 and 24 and arrange them in two columns (Sham Group or IMT Group). The secrecy of the allocation will be done in opaque and sealed envelopes. To ensure the blinding of the head researcher, this process will be performed by a member who will not be involved in the recruitment or development of the study. The study received approval from the Research Ethics Committee of the same institution (CAAE 64139317.5.0000.5479) and, was registered in Clinical Trials (NCT03186092). All participants received information's about procedures and the participants who agreed to participate will sign a statement of informed consent.

Patients will be selected based on the following eligibility criteria.

Inclusion criteria

- Patients with a diagnosis of PH (PAPm ≥ 25mmHg and PAOP <15mmHg);
- Patients of both genders and age greater than or equal to 18 years;
- Clinically stable with optimized and unchanged daily drug therapy in the last three months;
- Subjects who agree to participate in the research by signing a free and informed consent form.

Exclusion criteria

- Down syndrome;
- COPD;
- Severe ischemic heart disease;
- Left heart failure;
- Cor pulmonale;
- Cognitive disorders;
- Orthopedic problems;
- Emergency or elective surgical intervention during the protocol;
- Recent viral infections;
- Be included in a Rehabilitation program.

Sample Calculation

For this study was used the T-student test, where a significance level of 5% and a test power of 95% were adopted. Literature data were used and a minimum number (n) of 12 individuals per group was found based on maximal inspiratory pressure outcome[14] and distance walked on the six-minute walk test[15].

Evaluations and follow-up

After the selection of the patients and signing the consent form, the evaluations will be performed by physiotherapist who will be blinded to the allocation of the participants (Figure 1).

All participants will be submitted to evaluation to collect data such: gender, age (years), weight (kg), height (cm), PH etiology, right heart catheterization, functional class according to NYHA adapted to PH patients[13], oxygen therapy and medications in use.

Sample characterization

Evaluation to collect data such: gender, age (years), weight (kg), height (cm), PH etiology, right heart catheterization, functional class according to NYHA adapted to PH patients[17], oxygen therapy and medications in use. The participants will perform the evaluations in same day, with a time interval for rest.

Respiratory muscle strength

The MIP will be assessed using eletronic inspiratory muscle device *POWERbreath KH2* (*POWER breathe International Ltd. Warwickshire, England*). The patient should be relaxed, sitting and place the device in their mouth so that their lips form an airtight seal with the bacterial filter opening. The MIP will be measured near a residual volume after a maximal expiration

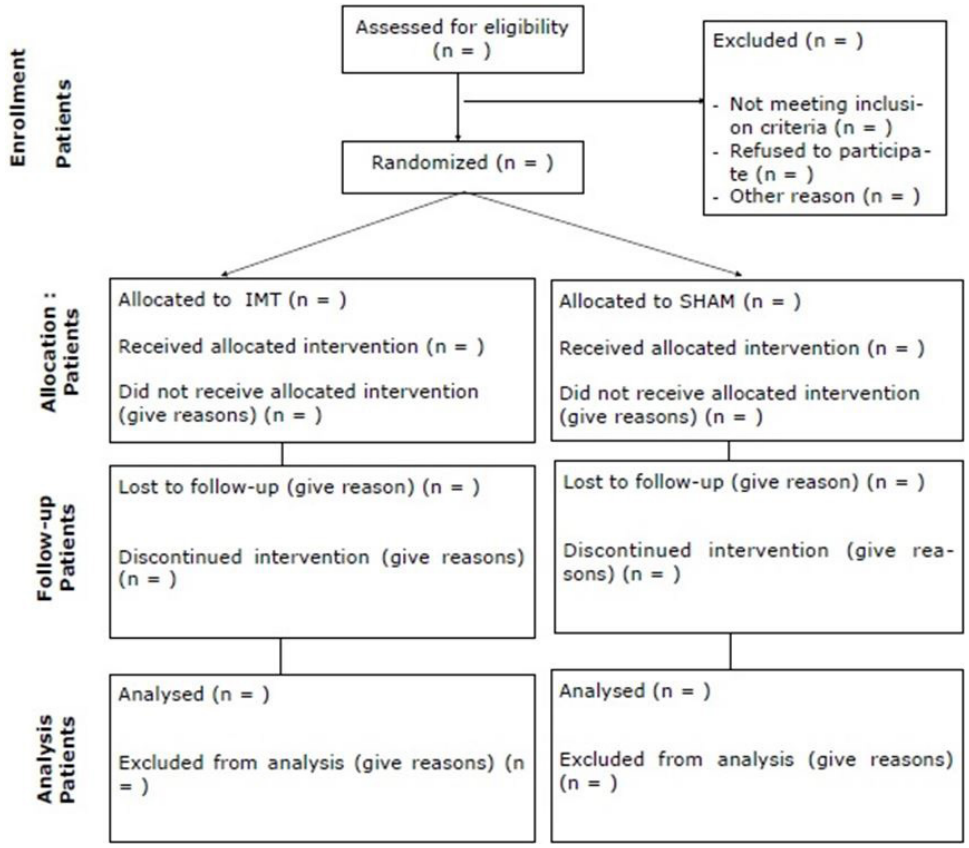

Figure 1. Modified CONSORT flow diagram for individual randomized controlled trials of nonpharmacologic treatments (CONSORT, 2017)[16].

with a rest interval of 1 minute. A total of 5 maneuvers will be performed, of which three will be accepted and, at least two, should present difference values of less than 10% of the highest value. The MIP percentages will be calculated as a percentage of their predicted values[18].

Endurance test (incremental protocol)

The patient breathing continuously through a mouthpiece connected to *POWERbreath* device with initial resistance of 50% of the MIP and 10% increments every 3 minutes until the participant is unable to continue breathing. As a result, the highest inspiratory pressure for at least 1 min will be taken as a measure of inspiratory muscle resistance (Pthmax).

Inspiratory resistance time (constant protocol)

The patient will breathe against a constant equivalent to 80% of Pthmax, resulting in time elapsed until task failure, defined as inspiratory resistance time (IRT)[19].

Six minute walk test

Functional capacity will be evaluated using a six-minute walk test (6MWT). It will be done following the American Thoracic Society Guidelines[20] in a 30-meter corridor. Will be mensured before, after and one minute after the end of the course: blood pressure (BP), heart rate (HR), respiratory rate (f), peripheral oxygen saturation (SpO_2) and breathlessness and fatigue perception will be determined using the Modified Borg Dyspnea Scale[21]. The examination will be performed under the guidance and control of the same physiotherapist, who will not accompany the patient during the walk. The participant will be instructed to walk as fast as possible for six minutes and will be encouraged with pre-established phrases at standardized one-minute intervals.

Quality of life questionnaire

To evaluate QoL, the Medical Outcomes Study 36-item Short Form Health Survey (Sf-36) will be applied. It was translated and validated into Portuguese using all the steps required by the expert committee, which addresses 36 self-health concepts that represent basic human values relevant to the functionality and well-being of each one, subdivided into eight dimensions, each with its own characteristic[22]. The participants will answer the questionnaire independently.

TREMMI Protocol:

Inspiratory muscle training Group

Is a home-based protocol. The treatment group will receive IMT using *POWERbreathe* Line Plus (*POWERbreathe* International Ltd. Warwickshire, England) 30% of MIP

30 minutes per day, 7 days per week, for 12 weeks, once one time per week with physiotherapy supervision. Participants will receive note diary to note the home-based training, the MIP will be measured every week by head researcher, and the resistance will adjust to maintain 30% of MIP.

SHAM Group:

The Control Group receive Sham IMT using *POWERbreathe* Line Plus without resistance spring for 30 minutes per day, 7 days per week, for 12 weeks. The SHAM Group will receive the same guidance, assessments and note diary of the IMT Group, an every week the MIP will be evaluated and a simulation of load adjustment by head researcher.

Both groups will be evaluated by respiratory muscle strength, functional capacity and quality of life questionnaire before, after and one month after the end of intervention.

Participants will have access to all information and will be allowed to withdraw from the study at any time without negative repercussions. In the case of urgency, the participants will be attended by ISCMSP.

STATISTICAL ANALYSIS

Data will be analyzed using the statistical software package SPSS version 13.1 (SPSS, Inc, Chicago, IL), the level of significance will be $p<0.05$. To analyze continuous variables will be used the Student t test, chi-square test for nominal data and the Mann-Whitney U test to ordinal data.

DISCUSSION

This paper provides a detailed description of a randomized, blinded clinical trial to determine the impact of the TREMMI protocol on functional capacity, respiratory muscle strength, and quality of life in patients with PH.

TRIAL STATUS

Patients are being recruited at the time of submission.

ACKNOWLEDGMENT

We are grateful to the support of the *Fundação de Amparo a Pesquisa do Estado de São Paulo* (FAPESP) of Faculdade de Ciências Médicas da Santa Casa de São Paulo, for the purchase of equipment used in the research.

AUTHOR'S CONTRIBUTION

MSL, RBJ and VLSA elaborated the study design; MSL and LMB performed the data collection; MSL, LMB, VLSA, RS and VBX performed the critical intellectual revision of the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

Nothing to declare.

AUTHOR DETAILS

[2] Universidade Federal de Santa Maria (UFSM), Santa Maria, RS, Brasil.

REFERENCES

1. American Thoracic Society. ATS Statement: guidelines for the six-minute walk test. Am J Respr Crit Care Med. 2002;166:111-7.
2. Babu AS, Padmakumar R, Maiya AG, Mohapatra AK, Kamath RL. Effects of Exercise Training on Exercise Capacity in Pulmonary Arterial Hypertension: A Systematic Review of Clinical Trials. Heart Lung Circ. 2016 Apr;25(4):333-41.
3. Bosnak-Guclu M, Arikan H, Savci S, Inal-Ince D, Tulumen E, Aytemir K, *et al*. Effects of inspiratory muscle training in patients with heart failure. Respir Med. 2011;105:1671-81.
4. Boutron I, Altman DG, Moher D, Schulz KF, Ravaud P. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. Annals of Internal Medicine. 2017;167(1):40–7.
5. Ciconelli RM, Ferraz MB, Santos W, Meinão I, Quaresma MR. Tradução para a língua portuguesa e validação do questionário genérico de avaliação de qualidade de vida SF-36 (Brasil SF-36). Revista Brasileira de Reumatologia. 1999;39(3):143-50.
6. Dall'Ago P, Chiappa GR, Guths H, Stein R, Ribeiro JP. Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. J Am Coll Cardiol. 2006;47(4):757-63.
7. Fowler RM, Gain KR, Gabbay E. Exercise intolerance in pulmonary arterial hypertension. Pulm Med. 2012;359:204:10.
8. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, *et al*. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2015; 37:67–119.
9. Galiè N, Simonneau G. The Fifth World Symposium on Pulmonary Hypertension. J Am Coll Cardiol. 2013;62:1–3.
10. Gosselink R, De Vos J, Van den Heuvel SP, Segers J, Decramer M, Kwakkel G. Impact of inspiratory muscle training in patients with COPD: what is the evidence?. Eur Respir J. 2011;37:416-25.
11. Hoeper MM, Bogaard HJ, Condliffe R, Frantz R, Khanna D, Kurzyna M, *et al*. Definitions and diagnosis of pulmonary hypertension. J Am Coll Cardiol. 2013;62:42–50.
12. Mainguy V, Maltais F, Saey D, Gagnon P, Martel S, Simon M, *et al*. Peripheral muscle dysfunction in idiopathic pulmonary arterial hypertension. Thorax. 2010;65:113–17.
13. Mereles D, Ehlken N, Kreuscher S, Ghofrani S, Hoeper M, Halank M, *et al*. Exercise and Respiratory Training Improve Exercise Capacity and Quality of Life in Patients With Severe Chronic Pulmonary Hypertension. Circulation. 2006;114:1482-89.
14. Meyer FJ, Borst MM, Zugck C, Kirschke A, Schellberg D, Kübler W, *et al*. Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. Circulation. 2001;103(17):2153–58.
15. Meyer FJ, Lossnitzer D, Kristen AV, Schoene AM, Kübler W, Katus HA, *et al*. Respiratory muscle dysfunction in idiopathic pulmonary arterial hypertension. Eur Respir J. 2005;25(1):125–130.
16. Muza SR, Silverman MT, Gilmore GC, Hellerstein HK, Kelsen SG. Comparison of scales used to quantitate the sense of effort to breathe in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1990; 141: 909–913.
17. Neder JA, Andreoni S, Lerario MC, Nery LE. Reference values for lung function tests. II. Maximal respiratory pressures and voluntary ventilation. Braz J Med Biol Res. 1999;32(6):719-27.
18. Panagiotou M, Peacock AJ, Johnson MK. Respiratory and limb muscle dysfunction in pulmonary arterial hypertension: a role for exercise training?. Pulm Circ. 2015;5:424–34.
19. Saglam M, Arikan H, Vardar-Yagli N, Calik-Kutukcu E, Inal-Ince D, Savci S, *et al*. Inspiratory Muscle Training in Pulmonary Arterial Hypertension. Journal of Cardiopulmonary Rehabilitation and Prevention.
20. Simonneau G, Galiè N, Lewis JR, Langleben D, Seeger W, Domenighetti G, *et al*. Clinical classification of pulmonary hypertension. Journal of the American College of Cardiology. 2004;43(12):S5-S12.

21. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, *et al*. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2013;62:34–41.

22. Vonk-Noordegraaf A, Haddad F, Chin KM, Forfia PR, Kawut SM, Lumens J, *et al*. Right heart adaptation to pulmonary arterial hypertension: physiology and pathobiology. J Am Coll Cardiol. 2013;62:22–33.